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(54) **Method for the conversion of arenes or alkenes with iodoalkenes, aryl iodides or arenediazonium salts**

(57) The invention relates to a method for the conversion of alkenes or arenes with iodoalkenes, aryl iodides or arenediazonium salts in the presence of hypophosphorous acid or its derivatives and a radical initiator.

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Description

[0001] The invention relates to a method for the conversion of alkenes or arenes with iodoalkenes, aryl iodides or arenediazonium salts in the presence of hypophosphorous acid or its derivatives and a radical initiator.

[0002] The inventive procedure is based on a typical radical reaction. These reactions are widely used in the formation of carbon-carbon bonds. There have been a number of useful procedures developed for reaction of radical intermediates. The key step in these procedures involves addition of a radical center to an unsaturated functional group. The radical formed by the reaction must then give rise to a new radical which can propagate the chain. An important group of such reactions involves halides as the source of the radical intermediate. The radicals are normally generated by halogen atom abstraction with a trialkylstannane as the reagent and an initiator such as azoisobutyronitrile (AIBN) or dibenzoylperoxide. The majority of radical reactions are based on tin hydrides as reducing agents and chain carriers, mainly tri-n-butyltin hydride (M. Pereyre, J.P.Quintard, A. Rahm, Tin in Organic Synthesis, Butterworths, London, 1986). However, organotin compounds are toxic and expensive and are difficult to remove completely from the desired reaction products. Alternative reagents such as tris(trimethylsilyl)silane (C. Chatgiliaoglu, Acc. Chem. Res., 1992, 25, 188) have been proposed, but these compounds are generally too expensive for carrying out radical reactions on an industrial scale.

[0003] It is known that radical reactions that replace certain functional groups by hydrogen, such as decarboxylations, deoxygenations, deaminations and dehalogenations are easily performed in the presence of tri-n-butyltin hydride. The reaction can also be carried out effectively when using commercially available and inexpensive hypophosphorous acid, its salts or dialkylphosphites, thus circumventing the disadvantages of tri-n-butyltin hydride (D. H. R. Barton, D. O. Jang, J. C. Jaszberenyi, J. Org. Chem. 1993, 58, 6838-6842, Tetrahedron Letters, 33, 39, 5709-5712, D. O. Jang, Tetrahedron Letters, 37, 30, 5367-5368, 1996).

[0004] However, there is still a demand to achieve carbon-carbon bond formation via radical reactions without the aid of expensive and toxic reagents such as tri-n-butyltin hydride or tris(trimethylsilyl)silane.

[0005] It was now found that hypophosphorous acid and its derivatives can also be used efficiently in place of tri-n-butyltin hydride or tris(trimethylsilyl)silane to achieve carbon-carbon bond formation via radical reactions.

[0006] Thus, the invention relates to a method for the conversion of alkenes or arenes with iodoalkenes, aryl iodides or arenediazonium salts in the presence of hypophosphorous acid or its derivatives and a radical initiator.

[0007] In particular, the invention relates to a method for the conversion of alkenes or arenes with iodoalkenes, aryl iodides or arenediazonium salts in the presence of hypophosphorous acid or its derivatives and a radical initiator, characterized in that the reacting alkenes and/or arenes are part of the same compound, thus performing an intramolecular carbon-carbon bond formation.

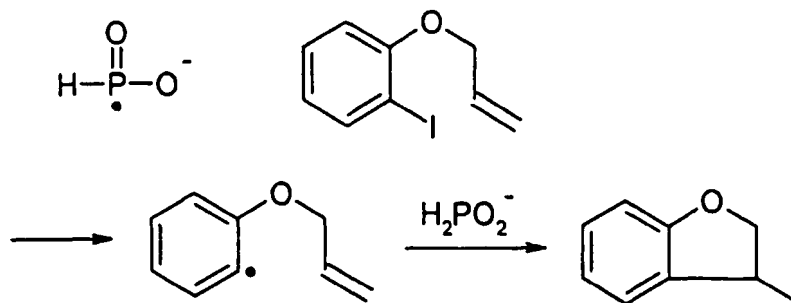
[0008] Alkenes also include heteroalkenes, preferably azaalkenes such as oximes. Arenes include heteroarenes such as pyridines or pyrimidines.

[0009] The expression diazonium, diazonium group or diazonium salt refers to all known diazonium salts such as e.g. diazonium tetrafluoroborate or chloride.

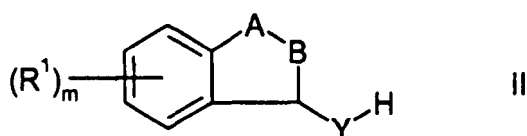
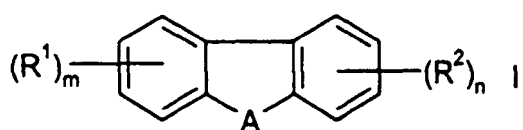
[0010] The radical reaction of the inventive procedure is assumed to start with hydrogen abstraction of the hypophosphorous acid or its derivative by the radical initiator as exemplified in the following scheme:



[0011] The radical then reacts with the iodoalkene or arene that is substituted by an iodo or a diazonium group. The organic radical thus formed adds to a double bond of an alkene or arene following known mechanisms:



15 **[0012]** The invention especially relates to a process for the manufacture of compounds of formulae I and II



wherein

35 R^1, R^2 are each, independently of one another, H, F, Br, Cl, CN, NO_2 , $\text{N}(\text{R}^3)_2$, OR^3 , SR^3 , COOR^3 , NHCOR^3 , SF_5 , SO_2R^3 or Alkyl having 1 to 12 carbon atoms which is unsubstituted or at least monosubstituted by F, Br, Cl, CF_3 or CN, wherein it is also possible for one or more non-adjacent $-\text{CH}_2-$ groups to be replaced, independently of one another, by $-\text{CH}=\text{CH}-$, $-\text{O}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{O}-$, $-\text{O}-$, $-\text{S}-$, $-\text{CO}-$, $-\text{O}-\text{CO}-$ or $-\text{CO}-\text{O}-$ or a mesogenic group,

40 R^3 H, alkyl or alkoxy having 1 to 12 carbon atoms or phenyl in which one or two CH-groups may also be replaced by N, which is unsubstituted or at least monosubstituted by F, Br, Cl, CF_3 , CN, NO_2 or alkyl or alkoxy having 1 to 12 carbon atoms,

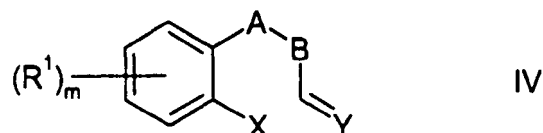
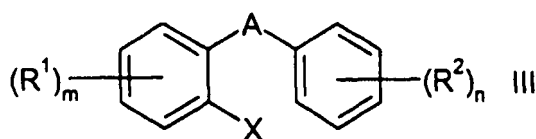
45 A, B are independently of one another, $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^3)-$, $-\text{N}=\text{C}(\text{R}^4)-$, $-\text{C}(\text{R}^4)=\text{N}-$, $-\text{C}(\text{R}^4)(\text{R}^5)-$, $-\text{C}(\text{R}^4)=\text{C}(\text{R}^5)-$, $-\text{C}(\text{R}^4)(\text{R}^5)\text{C}(\text{R}^6)(\text{R}^7)-$, $-\text{C}(\text{R}^4)(\text{R}^5)-\text{O}-$, $-\text{O}-\text{C}(\text{R}^4)(\text{R}^5)-$, $-\text{C}(\text{R}^4)(\text{R}^5)-\text{N}(\text{R}^3)-$ or $-\text{N}(\text{R}^3)-\text{C}(\text{R}^4)(\text{R}^5)-$, in such a way that heteroatoms are not linked directly to one another,

R^4, R^5, R^6, R^7 have independently of one another the meaning given for R^1 and R^2 ,

Y CR^4R^5 or NR^3

50 m, n 1, 2, 3 or 4,

by intramolecular reaction of the starting compounds III and IV



15 wherein

X is iodo or diazonium salt,

and

20 R^1 , R^2 , A, B, Y, m and n have the meaning given above, in the presence of hypophosphorous acid or its derivatives and a radical initiator.

[0013] Furthermore, the invention relates to the use of hypophosphorous acid or its derivatives in carbon-carbon bond forming radical reactions. It relates especially to the use of hypophosphorous acid or its derivatives in carbon-carbon bond forming radical cyclizations.

25 [0014] In a preferred embodiment of the invention R^1 and/or R^2 have the meaning of a mesogenic group of formula V



wherein

30 R^0 H, F, Br, Cl, CN, NO_2 , SF_5 or Alkyl having 1 to 12 carbon atoms which is unsubstituted or at least monosubstituted by F, Br, Cl, CF_3 or CN, wherein it is also possible for one or more non-adjacent $-CH_2-$ groups to be replaced, independently of one another, by $-CH=CH-$, $-O-CH=CH-$, $-CH=CH-O-$, $-O-$, $-S-$, $-CO-$, $-O-CO-$ or $-CO-O-$,

35 A^1 , A^2 are each, independently of one another,

a) trans-1,4-cyclohexylene in which one or two non-adjacent CH-groups may also be replaced by O or S,

b) 1,4-phenylene in which one or two CH-groups may also be replaced by N,

40 c) 1,3-cyclobutylene, 1,3-bicyclo(1,1,1)pentylene, 1,4-cyclohexenylene, 1,4-bicyclo(2,2,2)octylene, piperidine-1,4-diyl, naphthalene-2,6-diyl, decahydronaphthalene-2,6-diyl or 1,2,3,4-tetrahydronaphthalene-2,6-diyl,

45 wherein groups under a) and b) may be substituted by CN, F, Cl or Br,

Z^1 , Z^2 are each, independently of one another, $-CH_2CH_2-$, $-C=C-$, $-CH_2O-$, $-OCH_2-$, $-CO-O-$, $-O-CO-$, $-CH=N-$, $-N=CH-$, $-CH_2S-$ or $-SCH_2-$,
and

50 p is 0, 1, 2 or 3.

[0015] Above and below, R^0 , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , A, B, Y, X, A^1 , A^2 , Z^1 , Z^2 , p, m and n are as defined above, unless expressly stated otherwise. If the group R^1 appears more than once, it can have identical or different meanings.

55 The same applies to all other groups appearing more than once.

[0016] In compounds of formula I R^1 and/or R^2 are preferably Br, CN, NO_2 , $N(R^3)_2$, OR^3 , SR^3 , $COOR^3$, $NHCOR^3$, SO_2R^3 or Alkyl having 1 to 12 carbon atoms which is unsubstituted wherein it is also possible for one or more non-adjacent $-CH_2-$ groups to be replaced, independently of one another, by $-O-$, $-S-$, $-CO-$, $-O-CO-$ or $-CO-O-$ or a mesogenic

group of formula V. In especially preferred compounds of formula I R^1 and/or R^2 are Br, CN, NO_2 , $\text{N}(\text{R}^3)_2$, OR^3 , SR^3 , COOR^3 , NHCOR^3 , SO_2R^3 or a mesogenic group of formula V.

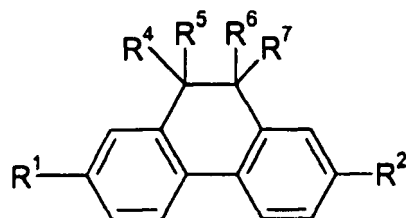
[0017] In compounds of formula II R^1 , R^4 , R^5 , R^6 and R^7 are preferably H, Br, CN, $\text{N}(\text{R}^3)_2$, OR^3 , SR^3 , COOR^3 , or Alkyl having 1 to 7 carbon atoms.

5 [0018] The preferred meaning of R^3 in compounds of formulae I and II is H or Alkyl or Alkoxy having 1 to 5 carbon atoms.

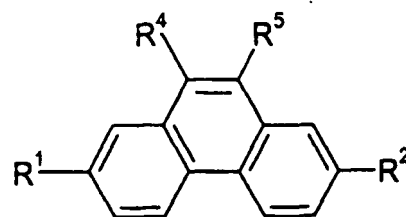
[0019] A is in compounds of formulae I and II preferably -O-, -S-, - $\text{N}(\text{R}^3)$ -, - $\text{C}(\text{R}^4)(\text{R}^5)$ -, - $\text{C}(\text{R}^4)=\text{C}(\text{R}^5)$ -, - $\text{C}(\text{R}^4)(\text{R}^5)\text{C}(\text{R}^6)(\text{R}^7)$ -, - $\text{C}(\text{R}^4)(\text{R}^5)\text{-O-}$ or - $\text{O-C}(\text{R}^4)(\text{R}^5)$ -. X is preferably iodo. Preferred meanings of m and n are 0, 1 or 2.

10 [0020] R^0 is preferably F, CN, CF_3 , OCF_3 , CHF_2 , OCF_2 , CHF_2 , OCHF_2 , OCF_2CF_3 , OCH_2CF_3 , OCHF_2CF_3 , SF_5 or Alkyl or Alkoxy, having 1 to 7 carbon atoms or Alkenyl or Alkenyloxy having 2 to 7 carbon atoms.

[0021] Preference is given to the compounds of the formulae I1 to I16 in the following group which can be obtained by the inventive process:



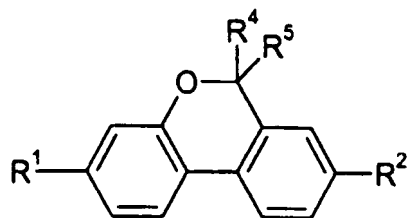
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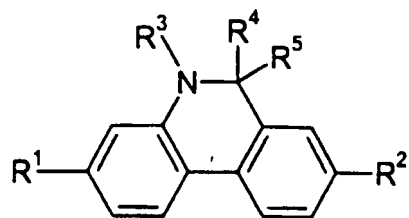
I2



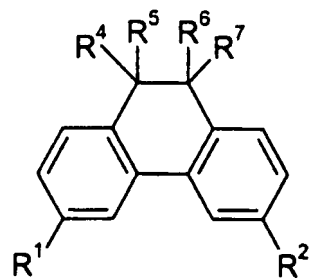
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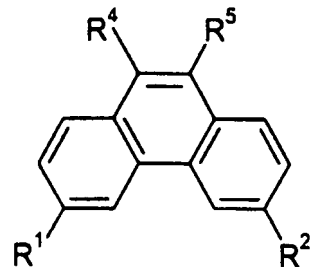
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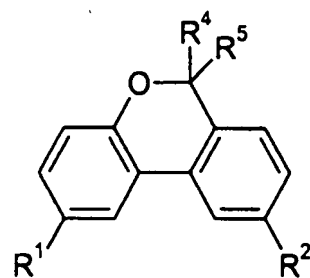
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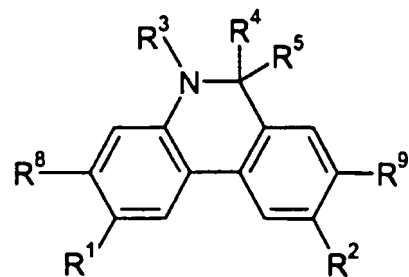
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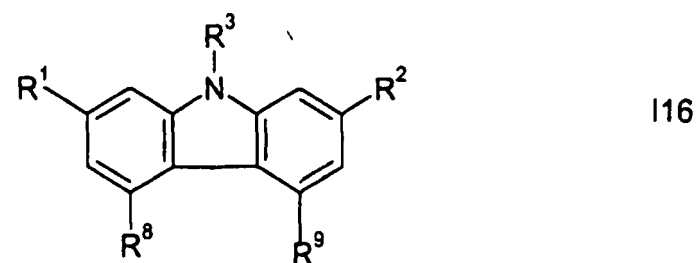
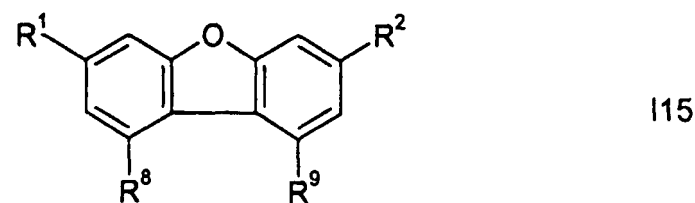
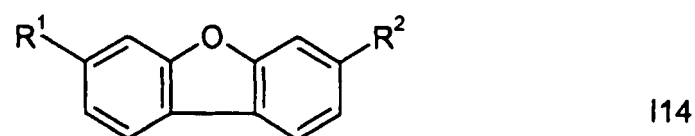
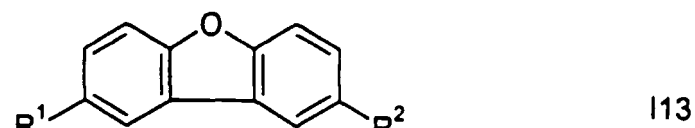
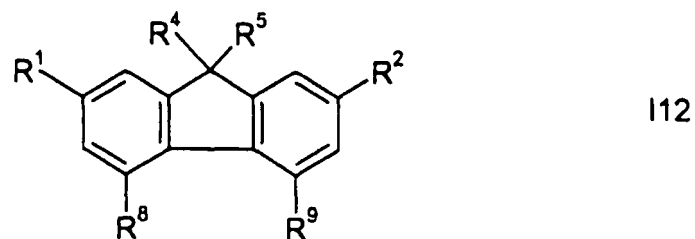
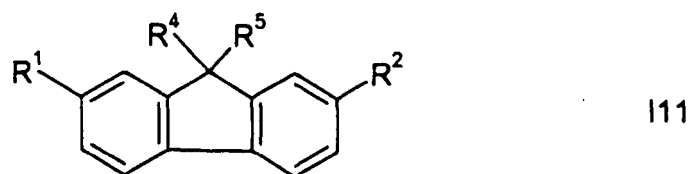
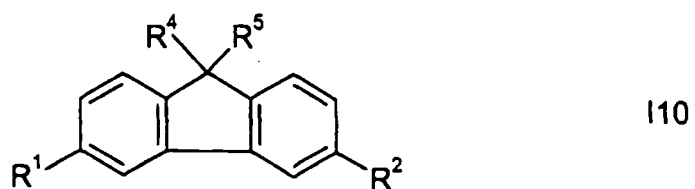
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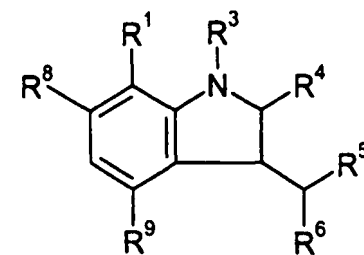
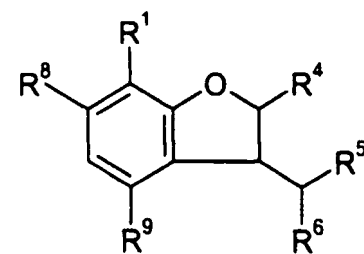
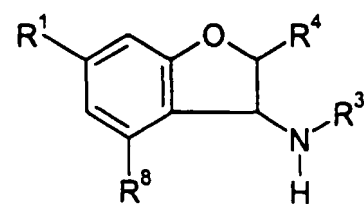
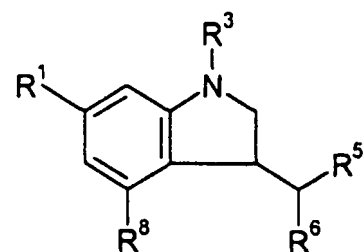
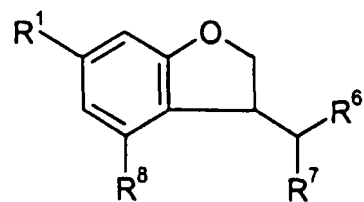
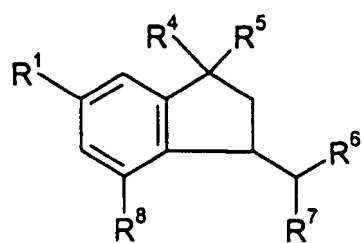
in which R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined above and R^8 and R^9 have the meaning given for R^1 and R^2 .

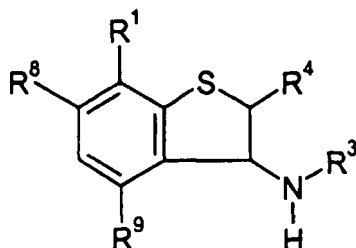
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[0022] Furthermore, preference is given to the compounds of the formulae I11 to I17 in the following group:

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in which R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined above and R^8 and R^9 have the meaning given for R^1 and R^2 .

[0023] Very particularly preferred compounds from these groups are those of formulae I1, I2, I3, I7, I10, I11, I12 and I16.

[0024] The compounds of formula I obtained in this way can be used for the synthesis of liquid crystal compounds and can readily be processed further to give a very wide variety of end products, e.g. by hydrogenation to give the corresponding saturated rings.

[0025] Compounds prepared by the inventive process may be used as products or intermediates in industrial organic chemistry, especially for applications in pharmaceutical or pesticide synthesis.

[0026] If R^1 , R^2 , R^4 , R^5 , R^6 , R^7 or R^0 in the formulae above and below is an alkyl group and/or alkoxy group, this can be straight-chain or branched. It is preferably straight-chain, has 2, 3, 4, 5, 6 or 7 carbon atoms and accordingly is preferably ethyl, propyl, butyl, pentyl, hexyl, heptyl, ethoxy, propoxy, butoxy, pentoxy, hexoxy or heptoxy, furthermore methyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, methoxy, octoxy, nonoxy, decoxy, undecoxy, dodecoxy, tridecoxy or tetradecoxy.

[0027] Oxaalkyl is preferably straight-chain 2-oxapropyl (= methoxymethyl), 2- (= ethoxymethyl) or 3-oxabutyl (= 2-methoxyethyl), 2-, 3- or 4-oxapentyl, 2-, 3-, 4- or 5-oxahexyl, 2-, 3-, 4-, 5- or 6-oxaheptyl, 2-, 3-, 4-, 5-, 6- or 7-oxaoctyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-oxanonyl, or 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-oxadecyl.

[0028] If R^1 , R^2 , R^4 , R^5 , R^6 , R^7 or R^0 is an alkyl group in which one CH_2 group has been replaced by $-\text{CH}=\text{CH}-$, this can be straight-chain or branched. It is preferably straight-chain and has 2 to 10 carbon atoms. Accordingly, it is in particular vinyl, prop-1- or -2-enyl, but-1-, -2- or -3-enyl, pent-1-, -2-, -3- or -4-enyl, hex-1-, -2-, -3-, -4- or -5-enyl, hept-1-, -2-, -3-, -4-, -5- or -6-enyl, oct-1-, -2-, -3-, -4-, -5-, -6- or -7-enyl, non-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-enyl, or dec-1-, -2-, -3-, -4-, -5-, -6-, -7-, -8- or -9-enyl. Alkenes having an E-double bond are preferred.

[0029] If R^1 , R^2 , R^4 , R^5 , R^6 , R^7 or R^0 is an alkyl group in which one CH_2 group has been replaced by $-\text{O}-$ and one has been replaced by $-\text{CO}-$, these are preferably adjacent. These thus contain one acyloxy group $-\text{CO}-\text{O}-$ or one oxycarbonyl group $-\text{O}-\text{CO}-$. These are preferably straight-chain and have 2 to 6 carbon atoms. Accordingly, they are in particular acetoxy, propionyloxy, butyryloxy, pentanoyloxy, hexanoyloxy, acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pentanoyloxymethyl, 2-acetoxyethyl, 2-propionyloxyethyl, 2-butyryloxyethyl, 3-acetoxypropyl, 3-propionyloxypropyl, 4-acetoxybutyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, propoxycarbonylmethyl, butoxycarbonylmethyl, 2-(methoxy-carbonyl)ethyl, 2-(ethoxy-carbonyl)ethyl, 2-(propoxy-carbonyl)ethyl, 3-(methoxy-carbonyl)propyl, 3-(ethoxy-carbonyl)propyl or 4-(methoxycarbonyl)butyl.

[0030] If R^1 , R^2 , R^4 , R^5 , R^6 , R^7 or R^0 is an alkyl group in which one CH_2 group has been replaced by unsubstituted or substituted $-\text{CH}=\text{CH}-$ and an adjacent CH_2 group has been replaced by CO or $\text{CO}-\text{O}$ or $\text{O}-\text{CO}-$, this can be straight-chain or branched. It is preferably straight-chain and has 4 to 13 carbon atoms. Accordingly, it is in particular acryloyloxymethyl, 2-acryloyloxyethyl, 3-acryloyloxypropyl, 4-acryloyloxybutyl, 5-acryloyloxypropyl, 6-acryloyloxyhexyl, 7-acryloyloxyheptyl, 8-acryloyloxyoctyl, 9-acryloyloxynonyl, 10-acryloyloxydecyl, methacryloyloxymethyl, 2-methacryloyloxyethyl, 3-methacryloyloxypropyl, 4-methacryloyloxybutyl, 5-methacryloyloxypropyl, 6-methacryloyloxyhexyl, 7-methacryloyloxyheptyl, 8-methacryloyloxyoctyl and 9-methacryloyloxynonyl.

[0031] If R^1 , R^2 , R^4 , R^5 , R^6 , R^7 or R^0 is an alkyl or alkenyl group which is monosubstituted by CN or CF_3 , this group is preferably straight-chain, and the substitution by CN or CF_3 is in the ω -position.

[0032] If R^1 , R^2 , R^4 , R^5 , R^6 , R^7 or R^0 is an alkyl or alkenyl group which is at least monosubstituted by halogen, this group is preferably straight-chain, and halogen is preferably F or Cl . In the case of multiple substitution, halogen is preferably F . The resulting groups also include perfluorinated groups. In the case of monosubstitution, the fluorine or chlorine substituent can be in any desired position, but is preferably in the ω -position.

[0033] Compounds of the formula I containing branched wing groups R^1 , R^2 , R^4 , R^5 , R^6 , R^7 or R^0 may occasionally be of importance due to better solubility in the customary liquid-crystalline base materials, but in particular as chiral dopes if they are optically active. Smectic compounds of this type are suitable as components for ferroelectric materials.

[0034] Branched groups of this type generally contain not more than one chain branch. Preferred branched groups

R^1 , R^2 , R^4 , R^5 , R^6 , R^7 or R^0 are isopropyl, 2-butyl (= 1-methylpropyl), isobutyl (=2-methylpropyl), 2-methylbutyl, isopentyl (=3-methylbutyl), 2-methylpentyl, 3-methylpentyl, 2-ethylhexyl, 2-propylpentyl, isopropoxy, 2-methylpropoxy, 2-methylbutoxy, 3-methylbutoxy, 2-methylpentoxy, 3-methylpentoxy, 2-ethylhexoxy, 1-methylhexoxy and 1-methylheptoxy.

[0035] The formulae I and II cover the racemates of these compounds and the optical antipodes, and mixtures thereof.

5 [0036] Of these compounds of the formula I, II and the sub-formulae, preference is given to those in which at least one of the groups present has one of the preferred meanings indicated.

[0037] The inventive procedure can be carried out preferably by dissolving the starting compounds in a suitable solvent under an inert gas atmosphere, adding hypophosphorous acid or its derivatives and a radical initiator and heating the mixture at a temperature of 30 to 200°C, preferably at 40 to 150°C, especially preferred at 45 to 130° until the reaction proceeds. In a preferred embodiment of the invention the reaction mixture is heated to the boiling point of the
10 respective solvent.

[0038] Preferred derivatives of hypophosphorous acid which can be used instead or in combination with hypophosphorous acid include for example salts of hypophosphorous acid such as alkali salts like sodium or potassium salts or addition salts of hypophosphorous acid and nitrogen bases like ammonia, trialkylamines such as triethylamine, tributylamine or triisooctylamine piperidine, n-alkylpiperidine such as n-ethylpiperidine, pyridine, pyrrolidine, imidazole, piperazine, cyclohexylamine, 2-aminoethanol, triethanolamine, aniline, n,n-dialkylaniline such as n,n-dimethylaniline, DABCO (1,4-diazabicyclo[2.2.2]octane), DBN (1,5-diazabicyclo[4.3.0]non-5-ene) or DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene). Also, dialkylphosphites such as dimethylphosphite, diethylphosphite, di-n-propylphosphite, diisopropylphosphite, di-n-butylphosphite, di-sec-butylphosphite, dipentylphosphite, [1,3,2]Dioxaphosphinane or
15 [1,3,2]Dioxaphospholane or dialkylphosphines such as dimethylphosphine, diethylphosphine, di-n-propylphosphine, diisopropylphosphine, di-n-butylphosphine, di-sec-butylphosphine dipentylphosphine, phospholane or phosphinane may be used.

[0039] Preferred solvents used for the inventive process are water, alcohols such as methanol, ethanol, n-propanol, i-propanol, n-butanol, i-butanol or t-butanol, sulfoxides such as dimethylsulfoxide or sulfolane, amides such as n,n-dimethylformamide or n-methylpyrrolidone, nitriles such as acetonitrile, ketones such as acetone, butanone, methylisopropylketone or methylisobutylketone, ethers such as diethylether methyl-tert-butylether, dioxane or tetrahydrofuran or anisole, esters such as methylacetate, ethylacetate, propylacetate or butylacetate, aromatic hydrocarbons such as benzene, toluene, xylenes or mesitylene, saturated hydrocarbons such as pentane, hexane, heptane, octane or cyclohexane or halogenated hydrocarbons such as dichloromethane, trichloromethane, dichloroethylene, trichloroethylene or fluorinated analogues or mixtures of the above mentioned solvents. Especially preferred solvents are water, alcohols such as methanol, ethanol, n-propanol, i-propanol, n-butanol, i-butanol or t-butanol, sulfoxides such as dimethylsulfoxide or sulfolane, amides such as n,n-dimethylformamide or n-methylpyrrolidone and nitriles such as acetonitrile or their mixtures.
25

In a particular preferred embodiment of the invention water or its mixtures with organic solvents is used.

35 [0040] The amount of solvent is not critical, in general 10 to 10000 g of solvent may be used for each g of starting material.

[0041] The inventive procedure is especially advantageous to be performed in water when using water soluble starting materials or materials that can be made water soluble by protonation or deprotonation as in the case with amines or carboxylic acids or sulfonic amides.

40 When water or a mixture containing water is used as a solvent in the inventive procedure, it may be advantageous to add tensides to the reaction mixture in order to achieve a better solubility of the starting material and the reagents and a higher reaction rate.

[0042] Depending on the type of starting material it may be necessary to add acids such as formic, acetic, hydrochloric or sulfuric acid or bases such as carbonates like sodium or potassium carbonate or sodium or potassium hydrogen-carbonate, hydroxides like sodium or potassium hydroxide or nitrogen containing bases such as ammonia, trialkylamines like triethylamine, tributylamine or triisooctylamine piperidine, n-alkylpiperidine like n-ethylpiperidine, pyridine, pyrrolidine, imidazole, piperazine, cyclohexylamine, 2-aminoethanol, triethanolamine, aniline, n,n-dialkylaniline like n,n-dimethylaniline, DABCO, DBN or DBU to the mixture of these compounds and the solvent in order to achieve a homogenous mixture and to ensure in the case when hypophosphorous acid or its salts are used, that the
45 hypophosphite anion stays unprotonated to an extent sufficient to perform the reaction.

50 [0043] The ratio of the molar amount of hypophosphorous acid or its derivatives to the molar amount of starting material is generally between 1 to 1 and 20 to 1, preferably between 2 to 1 and 15 to 1. In an especially preferred embodiment the ratio is between 5 to 1 and 10 to 1.

[0044] Preferably between 0.01 and 1.0 equivalents of a radical initiator are used in relation to hypophosphorous acid.

55 [0045] The reaction is preferably carried out in an intramolecular manner, i.e. the reaction centres (the iodoalkene, aryl iodide or arenediazonium salt and a double-bond of an alkene or arene that is not substituted by iodo or diazonium group) are part of the same molecule. In the case when the inventive procedure is not performed in an intramolecular manner, it may be advantageous to use the alkene or arene which is not substituted by iodo or diazonium group as sol-

vent, i.e. in a 10 to 1000-fold excess compared to the iodoalkene or iodo or diazonium substituted arene.

[0046] All known radical initiators can be employed in the inventive procedure. Preferred radical initiators are for example AIBN, dibenzoylperoxide, benzoylperoxide or di-tert-butylperoxide.

[0047] The time of reaction usually is in the range of one minute to 2 days, preferably between 0.1 and 20 hours.

[0048] The process according to the invention starts from readily accessible starting compounds which are prepared by methods known per se, as described in the literature (for example in the standard works such as Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), under reaction conditions which are known and suitable for said reactions.

[0049] Use can also be made here of variants which are known per se, but are not described here in greater detail.

[0050] In conclusion, hypophosphorous acid and its derivatives are effective radical reducing agents and are ideal alternatives to organotin or silicon hydrides in carbon-carbon bond forming reactions. They are inexpensive and less toxic than organotin hydrides. A simple work-up procedure can be applied for the purification of the products. The excess reagents and hypophosphorous-containing byproducts are washed out from the reaction mixture after radical reaction.

[0051] The examples below are intended to illustrate the invention without representing a limitation.

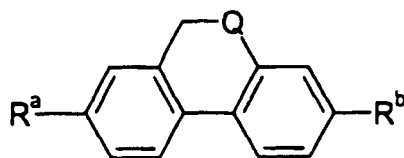
Example 1

[0052] A solution of O-allyl-3,5-diiodosalicylic acid (100 mg, 0.23 mmol, made by allylation of 3,5-diiodosalicylic acid methyl ester with allylic alcohol in the presence of triphenylphosphine and diisopropyl azodicarboxylate and subsequent saponification) in distilled water (5 ml) was treated with sodium hydrogen carbonate (193 mg, 2.3 mmol). This mixture was stirred in an inert atmosphere until a clear solution was obtained. Hypophosphorous acid (0.184 ml, 1.84 mmol) was added to this mixture. Once foaming had ceased the reaction was heated to reflux for 1 h. AIBN (40 mg/0.138 mmol) was added as a radical initiator in two portions over 30 mins. After addition of the second portion of initiator the reaction was heated at reflux for a further 15 h. On cooling to room temperature the reaction mixture was basified to pH 10 using 2M sodium hydroxide solution and extracted into dichloromethane. The aqueous layer was then acidified to pH 1 and extracted with dichloromethane. These organic layers were combined and dried over anhydrous magnesium sulfate before filtering and evaporating to dryness in vacuo. This yielded the cyclised product 3-methyl-2,3-dihydro-benzofuran-7-carboxylic acid as a fine white solid.


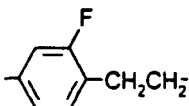
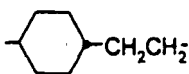
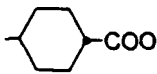
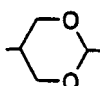
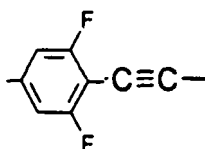
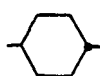
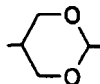
[0053] Accordingly, the following compounds are prepared from the respective starting materials by the inventive procedure:

Examples 2 to 17

[0054]

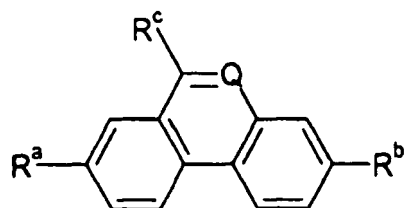



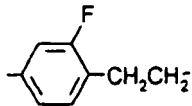
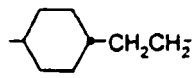
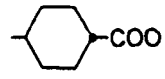
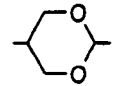
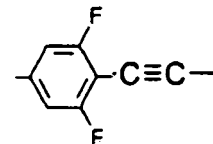
| | R ^a | R ^b | Q |
|-----|---------------------|------------------|-----------------|
| (2) | n-propyl | CN | CH ₂ |
| (3) | H ₂ C=CH | OCF ₃ | O |
| (4) | n-pentyl | n-propyl | CH ₂ |
| (5) | n-pentyloxy | n-propyl | CH ₂ |

| | | | | | |
|----|------|--|---|--------------------------------|---------------|
| | (6) | $\text{H}_2\text{C}=\text{CHCH}_2$ | | $\text{H}_2\text{C}=\text{CH}$ | O |
| | (7) | $\text{H}_2\text{C}=\text{CHCH}_2\text{O}$ | | F | CH_2 |
| 5 | (8) | n-propyl | | F | CH_2 |
| | (9) | n-butyl | | F | CH_2 |
| | (10) | n-propyl |  | OCF_3 | O |
| 10 | | | | | |
| | (11) | $\text{H}_2\text{C}=\text{CH}$ |  | OCF_3 | CH_2 |
| 15 | | | | | |
| | (12) | n-pentyl |  | F | CH_2 |
| 20 | | | | | |
| | (13) | n-pentyloxy |  | F | O |
| 25 | | | | | |
| | (14) | $\text{H}_2\text{C}=\text{CHCH}_2$ |  | CN | O |
| 30 | | | | | |
| | (15) | $\text{H}_2\text{C}=\text{CHCH}_2\text{O}$ |  | n-propyl | CH_2 |
| 35 | | | | | |
| | (16) | n-propyl |  | n-propyl | CH_2 |
| 40 | | | | | |
| | (17) | n-butyl |  | n-propyloxy | O |
| 45 | | | | | |
| | | | | | |
| 50 | | | | | |
| | | | | | |
| 55 | | | | | |

Examples 18 to 33

[0055]

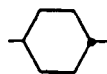


| | R ^a | | R ^b | Q | R ^c |
|------|--------------------------------------|---|---------------------|----|----------------|
| (18) | n-propyl | | CN | CH | H |
| (19) | H ₂ C=CH | | OCF ₃ | CH | H |
| (20) | n-pentyl | | n-propyl | CF | F |
| (21) | n-pentyloxy | | n-propyl | N | H |
| (22) | H ₂ C=CHCH ₂ | | H ₂ C=CH | CF | H |
| (23) | H ₂ C=CHCH ₂ O | | F | CH | H |
| (24) | n-propyl | | F | CH | F |
| (25) | n-butyl | | F | CH | H |
| (26) | n-propyl |  | OCF ₃ | CF | H |
| (27) | H ₂ C=CH |  | OCF ₃ | CH | H |
| (28) | n-pentyl |  | F | N | F |
| (29) | n-pentyloxy |  | F | CH | H |
| (30) | H ₂ C=CHCH ₂ |  | CN | CH | H |
| (31) | H ₂ C=CHCH ₂ O |  | n-propyl | N | H |

(32)

5

n-propyl



n-propyl

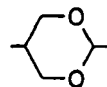
N

F

(33)

10

n-butyl



n-propyloxy

CH

H

15

20

25

30

35

40

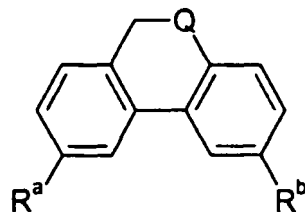
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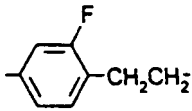
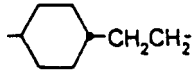
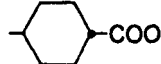
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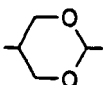
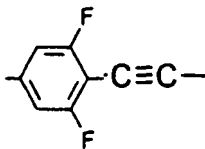
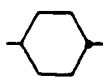
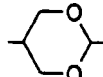
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Examples 34 to 49

[0056]

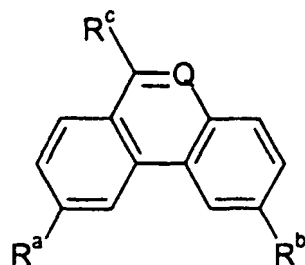


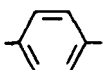
| | R ¹ | | R ² | Q |
|------|--------------------------------------|---|---------------------|-----------------|
| (34) | n-propyl | | CN | CH ₂ |
| (35) | H ₂ C=CH | | OCF ₃ | O |
| (36) | n-pentyl | | n-propyl | CH ₂ |
| (37) | n-pentyloxy | | n-propyl | CH ₂ |
| (38) | H ₂ C=CHCH ₂ | | H ₂ C=CH | O |
| (39) | H ₂ C=CHCH ₂ O | | F | CH ₂ |
| (40) | n-propyl | | F | CH ₂ |
| (41) | n-butyl | | F | CH ₂ |
| (42) | n-propyl |  | OCF ₃ | O |
| (43) | H ₂ C=CH |  | OCF ₃ | CH ₂ |
| (44) | n-pentyl |  | F | CH ₂ |
| (45) | n-pentyloxy |  | F | O |

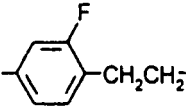
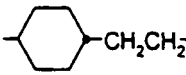
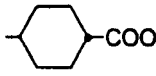
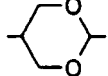
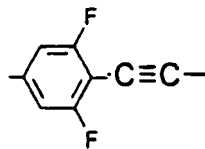
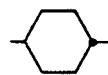
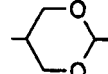
| | | | | |
|------|--|---|-------------|---------------|
| (46) | $\text{H}_2\text{C}=\text{CHCH}_2$ |  | CN | O |
| (47) | $\text{H}_2\text{C}=\text{CHCH}_2\text{O}$ |  | n-propyl | CH_2 |
| (48) | n-propyl |  | n-propyl | CH_2 |
| (49) | n-butyl |  | n-propyloxy | O |

Examples 50 to 65

[0057]

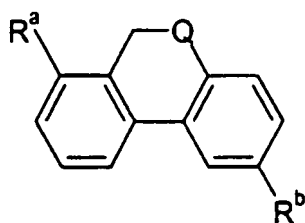


| | R^a | R^b | Q | R^c |
|------|--|---|----------------|--------------|
| (50) | n-propyl | CN | CH | H |
| (51) | $\text{H}_2\text{C}=\text{CH}$ | OCF_3 | CH | H |
| (52) | n-pentyl | n-propyl | CF | F |
| (53) | n-pentyloxy | n-propyl | N | H |
| (54) | $\text{H}_2\text{C}=\text{CHCH}_2$ | $\text{H}_2\text{C}=\text{CH}$ | CF | H |
| (55) | $\text{H}_2\text{C}=\text{CHCH}_2\text{O}$ | F | CH | H |
| (56) | n-propyl | F | CH | F |
| (57) | n-butyl | F | CH | H |
| (58) | n-propyl |  | OCF_3 | CF |

| | | | | | |
|------|--|---|----------------|----|---|
| (59) | $\text{H}_2\text{C}=\text{CH}$ |  | OCF_3 | CH | H |
| (60) | n-pentyl |  | F | N | F |
| (61) | n-pentyloxy |  | F | CH | H |
| (62) | $\text{H}_2\text{C}=\text{CHCH}_2$ |  | CN | CH | H |
| (63) | $\text{H}_2\text{C}=\text{CHCH}_2\text{O}$ |  | n-propyl | N | H |
| (64) | n-propyl |  | n-propyl | N | F |
| (65) | n-butyl |  | n-propyloxy | CH | H |

Examples 66 to 81

[0058]



15

| | R^a | R^b | Q |
|------|-------------|----------|--------|
| (66) | n-propyl | CN | CH_2 |
| (67) | $H_2C=CH$ | OCF_3 | O |
| (68) | n-pentyl | n-propyl | CH_2 |
| (69) | n-pentyloxy | n-propyl | CH_2 |

20

25

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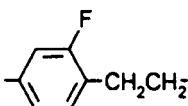
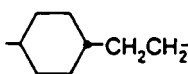
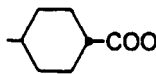
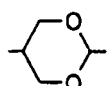
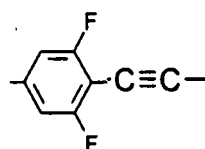
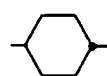
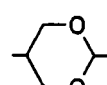
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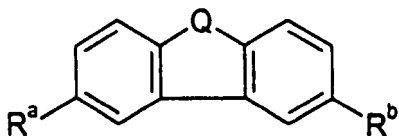
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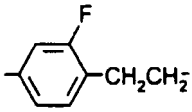
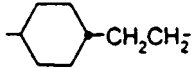
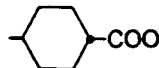
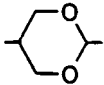
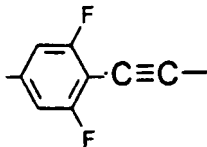
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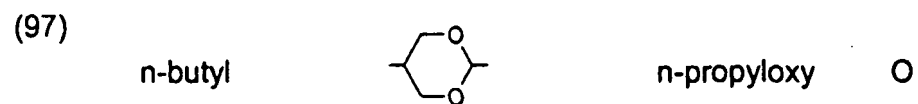
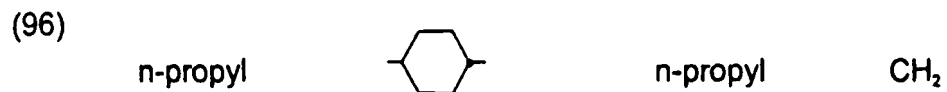
| | | | | | |
|----|------|--|---|--------------------------------|---------------|
| | (70) | $\text{H}_2\text{C}=\text{CHCH}_2$ | | $\text{H}_2\text{C}=\text{CH}$ | O |
| 5 | (71) | $\text{H}_2\text{C}=\text{CHCH}_2\text{O}$ | | F | CH_2 |
| | (72) | n-propyl | | F | CH_2 |
| | (73) | n-butyl | | F | CH_2 |
| 10 | (74) | n-propyl |  | OCF_3 | O |
| 15 | (75) | $\text{H}_2\text{C}=\text{CH}$ |  | OCF_3 | CH_2 |
| 20 | (76) | n-pentyl |  | F | CH_2 |
| 25 | (77) | n-pentyloxy |  | F | O |
| 30 | (78) | $\text{H}_2\text{C}=\text{CHCH}_2$ |  | CN | O |
| 35 | (79) | $\text{H}_2\text{C}=\text{CHCH}_2\text{O}$ |  | n-propyl | CH_2 |
| 40 | (80) | n-propyl |  | n-propyl | CH_2 |
| 45 | (81) | n-butyl |  | n-propyloxy | O |
| 50 | | | | | |
| 55 | | | | | |

Examples 82 to 97

[0059]

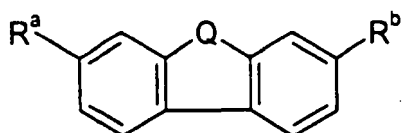



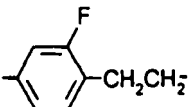
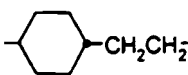
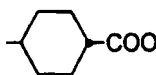
| | R^a | | R^b | Q |
|------|--------------------------------------|---|---------------------|-----------------|
| (82) | n-propyl | | CN | CH ₂ |
| (83) | H ₂ C=CH | | OCF ₃ | O |
| (84) | n-pentyl | | n-propyl | CH ₂ |
| (85) | n-pentyloxy | | n-propyl | CH ₂ |
| (86) | H ₂ C=CHCH ₂ | | H ₂ C=CH | O |
| (87) | H ₂ C=CHCH ₂ O | | F | CH ₂ |
| (88) | n-propyl | | F | CH ₂ |
| (89) | n-butyl | | F | CH ₂ |
| (90) | n-propyl |  | OCF ₃ | O |
| (91) | H ₂ C=CH |  | OCF ₃ | CH ₂ |
| (92) | n-pentyl |  | F | CH ₂ |
| (93) | n-pentyloxy |  | F | O |
| (94) | H ₂ C=CHCH ₂ |  | CN | O |
| (95) | H ₂ C=CHCH ₂ O |  | n-propyl | CH ₂ |

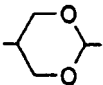
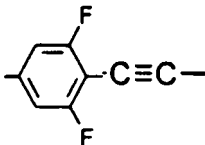
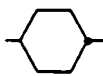
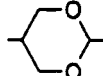


Examples 98 to 113

[0060]

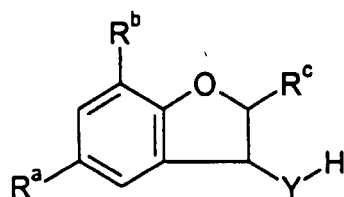


| | R ^a | | R ^b | Q |
|-------|--------------------------------------|---|---------------------|-----------------|
| (98) | n-propyl | | CN | CH ₂ |
| (99) | H ₂ C=CH | | OCF ₃ | O |
| (100) | n-pentyl | | n-propyl | CH ₂ |
| (101) | n-pentyloxy | | n-propyl | CH ₂ |
| (102) | H ₂ C=CHCH ₂ | | H ₂ C=CH | O |
| (103) | H ₂ C=CHCH ₂ O | | F | CH ₂ |
| (104) | n-propyl | | F | CH ₂ |
| (105) | n-butyl | | F | CH ₂ |
| (106) | n-propyl |  | OCF ₃ | O |
| (107) | H ₂ C=CH |  | OCF ₃ | CH ₂ |
| (108) | n-pentyl |  | F | CH ₂ |
| (109) | n-pentyloxy |  | F | O |

| | | | | | |
|----|-------|--|---|-------------|---------------|
| 5 | (110) | $\text{H}_2\text{C}=\text{CHCH}_2$ |  | CN | O |
| 10 | (111) | $\text{H}_2\text{C}=\text{CHCH}_2\text{O}$ |  | n-propyl | CH_2 |
| 15 | (112) | n-propyl |  | n-propyl | CH_2 |
| 20 | (113) | n-butyl |  | n-propyloxy | O |

25 Examples 114 to 124

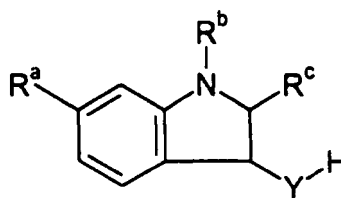
[0061]



| | R ^a | R ^b | R ^c | Y |
|-------|---------------------------------|----------------|----------------|----------------------------------|
| (114) | methyl | H | H | CH ₂ |
| (115) | methoxy | H | methyl | CH ₂ |
| (116) | phenyl | COOH | H | CHCH ₃ |
| (117) | CN | H | H | NOCH ₃ |
| (118) | NO ₂ | COOH | H | CH ₂ |
| (119) | SO ₂ CH ₃ | H | methyl | C(CH ₃) ₂ |
| (120) | H | COOH | H | CN |
| (121) | NHCOCH ₃ | H | H | CHCH ₃ |
| (122) | COOCH ₃ | COOH | methyl | CH ₂ |
| (123) | SC ₂ H ₅ | H | H | NOCH ₃ |
| (124) | H | COOH | H | CHCH ₃ |

Examples 125 to 134

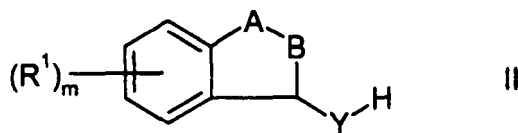
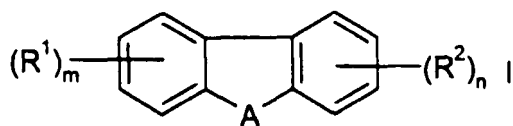
[0062]



| | R^a | R^b | R^c | Y |
|-------|--------------------------|----------------------------|-------|---------------------------|
| (125) | methyl | H | H | CH_2 |
| (126) | methoxy | COCH_3 | H | CH_2 |
| (127) | phenyl | SO_2CH_3 | H | CHCH_3 |
| (128) | CN | SO_2phenyl | H | NOCH_3 |
| (129) | NO_2 | OCH_3 | H | CH_2 |
| (130) | SO_2CH_3 | SO_2CH_3 | H | $\text{C}(\text{CH}_3)_2$ |
| (131) | OH | SO_2CH_3 | H | CN |
| (132) | NHCOCH_3 | COCH_3 | H | CHCH_3 |
| (133) | COOCH_3 | CH_3 | H | CH_2 |
| (134) | SC_2H_5 | H | H | NOCH_3 |

Claims

1. A method for the conversion of alkenes or arenes with iodoalkenes, aryl iodides or arenediazonium salts in the presence of hypophosphorous acid or its derivatives and a radical initiator.
2. A method according to claim 1, characterized in that the reacting alkenes and/or arenes are part of the same compound.
3. A process according to claim 2 for the manufacture of compounds of formulae I and II



wherein

R^1, R^2 are each, independently of one another, H, F, Br, Cl, CN, NO_2 , $\text{N}(\text{R}^3)_2$, OR^3 , SR^3 , COOR^3 , NHCOR^3 , SF_5 , SO_2R^3 or Alkyl having 1 to 12 carbon atoms which is unsubstituted or at least monosubstituted by F, Br, Cl, CF_3 or CN, wherein it is also possible for one or more non-adjacent $-\text{CH}_2-$ groups to be replaced, independently of one another, by $-\text{CH}=\text{CH}-$, $-\text{O}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{O}-$, $-\text{O}-$, $-\text{S}-$, $-\text{CO}-$, $-\text{O}-\text{CO}-$ or $-\text{CO}-\text{O}-$ or a mesogenic group,

R^3 H, alkyl or alkoxy having 1 to 12 carbon atoms or phenyl in which one or two CH-groups may also be replaced by N, which is unsubstituted or at least monosubstituted by F, Br, Cl, CF_3 , CN, NO_2 or alkyl or alkoxy having 1 to 12 carbon atoms,

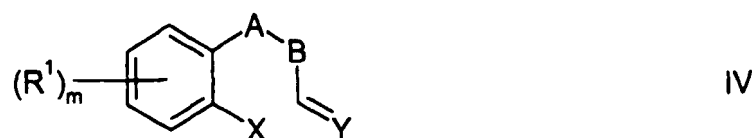
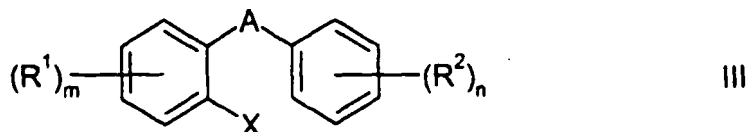
A, B are independently of one another, $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^3)-$, $-\text{N}=\text{C}(\text{R}^4)-$, $-\text{C}(\text{R}^4)=\text{N}-$, $-\text{C}(\text{R}^4)(\text{R}^5)-$, $-\text{C}(\text{R}^4)=\text{C}(\text{R}^5)-$, $-\text{C}(\text{R}^4)(\text{R}^5)\text{C}(\text{R}^6)(\text{R}^7)-$, $-\text{C}(\text{R}^4)(\text{R}^5)-\text{O}-$, $-\text{O}-\text{C}(\text{R}^4)(\text{R}^5)-$, $-\text{C}(\text{R}^4)(\text{R}^5)-\text{N}(\text{R}^3)-$ or $-\text{N}(\text{R}^3)-\text{C}(\text{R}^4)(\text{R}^5)-$ in such a way that heteroatoms are not linked directly to one another,

R^4, R^5, R^6, R^7 have independently of one another the meaning given for R^1 and R^2 ,

Y CR^4R^5 or NR^3

m, n 1, 2, 3 or 4,

by intramolecular reaction of the starting compounds III and IV



wherein

X is iodo or diazonium salt,

and

R^1, R^2, A, B, Y, m and n have the meaning given above, in the presence of hypophosphorous acid or its derivatives and a radical initiator.

4. The process of claim 3, wherein R^1 and/or R^2 have the meaning of a mesogenic group of formula V



wherein

R^0 H, F, Br, Cl, CN, NO_2 , SF_5 or Alkyl having 1 to 12 carbon atoms which is unsubstituted or at least monosubstituted by F, Br, Cl, CF_3 or CN, wherein it is also possible for one or more non adjacent $-\text{CH}_2-$ groups to be replaced, independently of one another, by $-\text{CH}=\text{CH}-$, $-\text{O}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{OH}-\text{O}-$, $-\text{O}-$, $-\text{S}-$, $-\text{CO}-$, $-\text{O}-\text{CO}-$ or $-\text{CO}-\text{O}-$,

A^1, A^2 are each, independently of one another,

a) trans-1,4-cyclohexylene in which one or two non-adjacent CH-groups may also be replaced by O or S,

b) 1,4-phenylene in which one or two CH-groups may also be replaced by N,

c) 1,3-cyclobutylene, 1,3-bicyclo(1,1,1)pentylene, 1,4-cyclohexenylene, 1,4-bicyclo(2,2,2)octylene, piperidine-1,4-diyl, naphthalene-2,6-diyl, decahydronaphthalene-2,6-diyl or 1,2,3,4-tetrahydronaphthalene-2,6-diyl,

wherein groups under a) and b) may be substituted by CN, F, Cl or Br,

Z^1, Z^2 are each, independently of one another, $-CH_2CH_2-$, $-C=C-$, $-CH_2O-$, $-OCH_2-$, $-CO-O-$, $-O-CO-$, $-CH=N-$, $-N=CH-$, $-CH_2S-$ or $-SCH_2-$, and

p is 0, 1, 2 or 3.

5. Process according to claim 1 to 4, characterized in that the starting compounds and hypophosphorous acid or its derivatives are heated in the presence of a radical initiator at a temperature of 30 to 200°C.
6. Process according to claim 1 to 5, wherein hypophosphorous acid its salts, dialkylphosphites or dialkylphosphines are used as reagent.
7. Process according to claim 1 to 6, wherein water or its mixture with organic solvents is used.
8. Process according to claim 1 to 7, wherein AIBN, dibenzoyperoxide, benzoylperoxide or di-tert-butylperoxide are used as radical initiators.
9. Use of hypophosphorous acid or its derivatives in carbon-carbon bond forming radical reactions.
10. Use of hypophosphorous acid or its derivatives in carbon-carbon bond forming radical cyclizations.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 99 11 6091

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | |
|---|--|--|--|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int.Cl.7) |
| X | WO 97 42194 A (GLAXO WELLCOME) 13 November 1997 (1997-11-13) page 1, line 14 to page 2, line 18; page 11, lines 25-33 --- | 9,10 | C07B37/10 C07B37/04 |
| D,A | D. H. R. BARTON: "The invention of radical reactions. 32. Radical deoxygenations, dehalogenations, and deaminations with dialkyl phosphites and hypophosphorous acid as hydrogen sources" JOURNAL OF ORGANIC CHEMISTRY, vol. 58, no. 24, 19 November 1993 (1993-11-19), pages 6838-6842, XP002122647 EASTON US * tables III-VI * | 1 | |
| D,A | C. CHATGILIALOGLU: "Organosilanes as radical-based reducing agents in synthesis" ACCOUNTS OF CHEMICAL RESEARCH., vol. 25, no. 4, April 1992 (1992-04), pages 188-194, XP002122648 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0001-4842 * page 191, column 2 - page 192, column 1 * | 1 | TECHNICAL FIELDS SEARCHED (Int.Cl.7) C07B |
| P,X | S. R. GRAHAM: "Hypophosphite mediated carbon-carbon bond formation: a clean approach to radical methodology" TETRAHEDRON LETTERS, vol. 40, no. 12, 19 March 1999 (1999-03-19), pages 2415-2416, XP002122649 OXFORD GB * the whole document * | 1-3,5,6,8-10 | |
| The present search report has been drawn up for all claims | | | |
| Place of search THE HAGUE | | Date of completion of the search 15 November 1999 | Examiner Wright, M |
| <p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p> | | | |

EPO FORM 1503 03/92 (P04C01)

